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TITLE:
Linuron: Waiver Request for a 28-Day Inhalation Toxicity Study

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OPPTS Guideline 870.3465 90 Day Inhalation Toxicity

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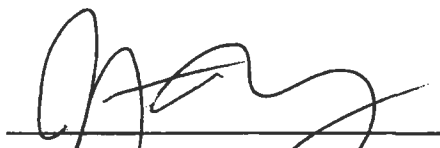

Feb 13, 2012

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Date

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STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

This report is a waiver request for no further testing. Good Laboratory Practice Standards, 40 CFR Part 160, are not applicable to this submission.

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TABLE OF CONTENTS

	Page No.
Statement of No Data Confidentiality Claims	2
Good Laboratory Practice Statement	3
Introduction	5
Linuron has been Previously Tested in Repeat Dose Toxicity Studies	6
Fourteen-day Rat Inhalation Study	6
29-Day Inhalation Study	7
Conclusions	7
A Waiver for the Linuron Repeat Dose Study Should be Granted Based on EPA Inhalation Toxicity Waivers Guidance	8
Additional Inhalation Toxicity Data Will Not Impact Risk Assessments of Linuron	10
Conclusions	10

Linuron: Waiver Request for 28-Day Inhalation Toxicity Study (OPPTS 870.3465)

Introduction

In its Human Health Assessment Scoping Document in Support of Registration Review on Linuron[1] (Scoping Document) and in a Data Call In Notice date October 17, 2011, USEPA (Agency) required the conduct of a repeat dose inhalation toxicity study in rats. In the Scoping Document, the Agency did not indicate a rationale for requiring this study. According to the new 40CFR Part 158 data requirement, a 90-day inhalation toxicity study is a conditional requirement. This study is required if there is the likelihood of significant repeated inhalation exposure to the pesticide as a gas, vapor or aerosol. The Agency further states that studies of shorter duration, e.g., 21- or 28-days may be sufficient to satisfy this requirement based on estimates of the magnitude and duration of human exposure. In the case of Linuron, the Agency is requesting a 28-day study per footnote 12 of the DCI.

In its guideline (OPPTS 870.3465) for a 90-day inhalation toxicity study, the Agency indicates the following under the purpose for this study:

> It can provide useful information on health hazards likely to arise from repeated exposures by the inhalation route over a limited period of time. It will provide information on target organs and the possibilities of accumulation, and can be of use in selecting dose levels for longer-term studies and for establishing safety criteria for human exposure. Hazards of inhaled substances are influenced by the inherent toxicity and by physical factors such as volatility and particle size.

The guideline goes on to say that "[e]xtrapolation from the results of this study to humans is valid only to a limited degree", indicating the unreliability of the extrapolation methodology.

TKI requests that the USEPA revisit the requirement for this study; TKI believes the repeat dose inhalation study should not be required based on USEPA guidance for inhalation waivers and the following Linuron specific rationale:

1. Linuron has favorable acute inhalation toxicity characteristics. In the Scoping Document, the Agency indicates Linuron is Toxicity Category IV for acute inhalation toxicity.
2. Linuron has a low vapor pressure and is not anticipated to be available for inhalation exposure;
3. The applications methods minimize inhalation exposure. Linuron is a pre and early post emergence herbicide that is applied by ground equipment at low pressure, high water volume, and large droplet sizes. There are no aerial or airblast application uses labeled for Linuron containing formulations.

[1] EPA (2010) Linuron: Addendum to the Human Health Assessment Scoping Document in Support of Registration Review. Memorandum dated May 28, 2010 from Kristin Rury, Steve Funk and Whang Phang, Risk Assessment Branch 3 (Health Effects Division) to Tom Myers/Katherine St. Clair, Risk Management and Implementation Branch II (Pesticide Re-Evaluation Division).

4. Linuron meets the criteria presently listed by EPA for waiving a repeated dose inhalation toxicity study. It also meets a criterion not listed but indicated by EPA to be a reason for granting a waiver.
5. The toxicity of linuron has been well characterized. The systems affected to the greatest degree are the hematopoetic and endocrine.
6. An additional repeated dose inhalation toxicity study will not provide any new or more relevant information toward refining occupational risk assessments for inhalation exposure.
7. According to the reregistration evaluation document (RED) for Linuron[2], the MOEs for occupational exposure are driven by the dermal exposure to Linuron and not by inhalation exposure.
8. A 14-day repeat dose inhalation studies has already been submitted to the USEPA. An additional 29-day repeated dose study from the public literature has reported consistent NOELs and LOELs with the submitted 14-day study.
9. From an animal welfare standpoint, the conduct of an additional inhalation toxicity study would be an inappropriate use of additional animals.

Linuron has Been Previously Tested in Repeat Dose Toxicity Studies

TKI is aware of the existence of two repeated dose inhalation toxicity studies conducted in rats on linuron. The first study (14-day repeated dose) was conducted in 1981 by Haskell Laboratories. The NOEL was considered to be 0.058 mg/L (based on body weight estimates, this equates to approximately 15 -19 mg/kg/day) based on increased blood urea nitrogen and urine volume observed at 0.24 and 0.99 mg/L. This study does not meet the requirements of the 28-day inhalation toxicity study guideline; however, it does provide valuable information about the inhalation toxicity of linuron. TKI also located a second study (29-day repeated dose) in the public literature that was conducted in 1989. The NOEL in this study was considered to be 0.08 mg/L (based on body weight estimates, this equates to approximately 20 - 26mg/kg/day) based on decreased body weight and effects on hematology and clinical chemistry parameters observed at 0.4 mg/L. The NOELs found in the 14-day and 29-day studies are consistent indicating that the increased study length had no effect on the NOEL. The results of each of these studies are summarized below.

Fourteen-day rat inhalation study. A 14-day inhalation toxicity study on linuron (95.3% purity) was conducted in 1981 by Haskell Laboratory for Health and Environmental Science (MRID 46612101) which has been submitted to EPA[3]. In this study, groups of 10 male Crl:CD rats were exposed nose-only for 6 hours/day, 5 days/week to concentrations of 0, 0.058, 0.24 or 0.99 mg/L of linuron (mean measured concentrations). The mass median aerodynamic diameter (MMAD) was determined to be 2.5 to 4.8 μm. After exposure, rats exposed to 0.99 mg/L showed weakness and loss of coordination. The loss of coordination could have been a result of the combination of restraint and systemic toxicity of the test

[2] EPA (1995) Reregistration Eligibility Decision (RED): Linuron. http://www.epa.gov/oppsrrd1/REDs/0047.pdf
[3] Ferenz, R. (1981 study completion; 2005 study report revision 1) Linuron: Two-week inhalation toxicity study in male rats. E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Enviornmental Sciences. Laboratory Project ID: HLR-81-81. Unpublished study.

substance. These types of effects have not been observed in other toxicity studies with linuron, where different routes of administration and no restrainers were used. There were no treatment-related effects on hematology, clinical chemistry and urinalysis parameters at 0.058 mg/L. Rats exposed to 0.24 and 0.99 mg/L had decreased blood urea nitrogen and had larger urine volumes and more dilute urine than the controls. Rats exposed to 0.99 mg/L also showed increased neutrophils, decreased lymphocytes and elevated alanine aminotransferase activity compared to the control group. These effects were found to be completely reversed 13 days post exposure. There were no microscopic findings in the tissues examined. However, absolute thymus weights were significantly lower in rats exposed to 0.99 mg/L compared to controls, and relative liver weights were significantly higher than controls in all test groups. No significant differences were seen following the 13-day recovery period. The NOEL was considered to be 0.058 mg/L. This study does not meet the requirements of the 28-day inhalation toxicity study guideline; however, it does provide valuable information about the inhalation toxicity of linuron.

29-Day Inhalation Study. TKI is also aware of another repeated dose inhalation toxicity study in rats. This study was summarized in a monograph prepared for the European Union by the rapporteur member state, the United Kingdom in a monograph dated October 1996[4]. The study was conducted in 1989. In this study, Wistar rats were exposed to linuron (nose only) at dosage levels (mean measured) of 0, 0.013, 0.08 or 0.4 mg/L to 15, 10, 15 and 15 rats/sex, respectively for 29 days (6 hours/day for 5 days/week). The MMAD for the three dose groups ranged between 1.0 to 4.7 µm. Ten animals/sex were sacrificed one day after the final exposure. The remaining animals were sacrificed 29 days after the final exposure. There were no deaths during the study. At 0.4 mg/L, animals exhibited uncoordinated gait (as noted in the above study) and ruffled fur during exposure. Weight gain was statistically significantly decreased at the high dose in male rats. Food consumption was unaffected by treatment. A statistically significant decrease in mean erythrocyte count in both sexes, an increase in mean reticulocyte count in both sexes, a slight increase in mean corpuscular volume in females and, a slight decrease in mean activate partial thromboplastin time in males at 0.4 mg/L only were observed. ALT and AST (females only) activities, total bilirubin and total lipid concentrations were statistically increased at 0.4 mg/L. Decreases in mean serum glucose levels and α_2-globulin levels were observed at doses of $\geq$0.08 mg/L. Relative liver weights were slightly increased and pituitary weight (absolute and relative) were decreased in females at the high dose. No macroscopic or microscopic findings were observed. In the absence of any microscopic findings, the effects on glucose and α_2-globulin levels were considered to be of no toxicologic significance. The NOAEL was considered to be 0.08 mg/L.

Conclusions. The NOELs found in the 14-day and 29-day studies are consistent indicating that the increased study length had no effect on the observed NOEL. The LOEL in the 14-day study was 0.24 mg/L and 0.4 mg/L in the 29-day study. Microscopic findings were not observed in the lung in either study nor in any other tissue examined.

[4] European Commission. Peer Review Programme. ECCO-Meetings. Linuron Volume 3. Annex B. Rapporteur Member State: United Kingdom. October 1996.

The toxicity characteristics of linuron have been well documented by the oral route in various test species. Orally, the hematopoetic and endocrine systems are most sensitive to the effects of linuron. The effects observed in the hematopoetic system are increased methemoglobin in dogs and mice and hemosiderosis in the bone marrow, spleen and/or lymph nodes of rats (evidence of hemolytic anemia) and mice. The dog was the most sensitive species with a NOEL for these effects of 0.77 mg/kg/day.

Linuron has been shown to be a weak androgen antagonist in several test systems. In addition, in a rat reproduction study, macroscopic findings included increased incidences of small testes and epididymides and deformed epididymides in parental males with a NOEL of 5.8 mg/kg/day and a LOEL of 36 mg/kg/day[1].

No microscopic findings were observed in the tissues examined in either repeated dose inhalation study summarized above. Decreased erythrocyte count was observed in rats in the 29-day study at the highest dose tested (0.4 mg/L) indicating some concordance between the two routes of exposure for the effects of linuron on the hematopoietic system.

The Hazard Identification Assessment Review Committee selected the NOEL (5.8 mg/kg/day) for reduced body weights during the premating period from the rat reproduction study for short-term (1-30 days) inhalation exposure[5]. The lowest NOEL (0.24 mg/L) from the inhalation studies summarized above can be used by EPA in a revised risk assessment to determine if it would alter the risk assessment to a significant degree, a more conservative degree then using the NOEL from the rat reproduction study. Therefore, these studies provide sufficient information to address EPAs questions regarding the inhalation toxicity of linuron negating a need for additional inhalation testing. Any further testing would be an inappropriate use of test animals.

A Waiver for the Linuron Repeat Dose Study Should be Granted Based on EPA Inhalation Toxicity Waivers Guidance

USEPA provided registrants guidance on the acceptability criteria for inhalation toxicity waivers[6], and TKI believes that linuron meets some of these criteria. In addition to the four criteria listed, this document also indicates that if no significant inhalation hazard is identified during risk characterization and risk assessment, HED may also initiate a waiver. The four criteria are listed and discussed below in relation to linuron.

Severe irritation and corrosivity. Linuron does not meet this criterion because it is neither a severe irritant nor corrosive.[2]

[5] EPA (2001) Linuron: Report of the Hazard Identification Assessment Review Committee. HED Doc. No. 0050286 dated November 20, 2001.

[6] EPA (2002) Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies. Memorandum dated August 15, 2002 from Margaret Stasikowki to the Health Effects Division Staff.

Low volatility. According to the EPA discussion for this criterion, a non-volatile active ingredient is defined as having a vapor pressure of $<7 \times 10^{-4}$ mm Hg for outdoor uses. The vapor pressure of linuron is 1.5×10^{-5} mm Hg.

Large aerosol particle size. Particle size studies have not been performed on the linuron formulations supported by TKI. However, based on the labeled application methods (ground application, high volume), particle sizes are predicted to be large. Note that aerial applications are not allowed with end use products containing linuron.

Toxicity category IV and extrapolated MOE. Linuron has reported LC_{50} values of 1.7 mg/L to 6.15 mg/L (see discussion below). In addition, a robust toxicology database of repeated dose oral studies exists on linuron which could be used for extrapolating an MOE.

TKI understands that these criteria for a waiver are under reconsideration by EPA; however, it would like to point out the following concerning the characteristics of linuron:

- Linuron has favorable inhalation toxicity characteristics. The LC_{50} for linuron according to the RED is >1.7 mg/L. Four hour LC_{50}s of >4.06 mg/l[7] and 6.15 mg/L[8] have also been reported indicating that linuron is not toxic by this route of exposure. In its scoping document[1], EPA indicates that linuron is toxicity category IV for inhalation toxicity,
- Linuron has a low vapor pressure and exposure via inhalation is negligible. In the 1995 RED[3], EPA indicated that the "vapor pressure for linuron was 1.5×10^{-5} mm Hg at 24°C; therefore, volatilization and subsequent photodegradation in air are not considered probable routes of dissipation". The present application methods minimize inhalation exposure. The only registered formulations of linuron are a flowable concentrate and a dry flowable. Both of these formulations result in reduced inhalation exposure compared to other formulations, such as wettable powders. In addition, there are no aerial or airblast applications allowed by label. Application is by ground boom or chemigation or ground boom.
- The RED did not identify any inhalation risk associated with the application procedures allowed by label for the TKI linuron registered products. The unit dermal exposure versus the unit inhalation exposure was 0.014 versus 0.0004 mg/lb a.i. or 1:0.028.

In conclusion, linuron meets the criteria of the present EPA criteria for granting a waiver request for a repeated dose inhalation study. In addition, no inhalation risk was identified in the RED associated with the application procedures allowed by label for the formulations supported by TKI which meets the additional reason for which EPA will entertain a waiver request.

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[7] Hartley, D. and H. Kidd (eds.). The Agrochemicals Handbook. 2nd ed. Lechworth, Herts, England: The Royal Society of Chemistry, 1987., p. A248/Aug 87.

[8] Weed Science Society of America. Herbicide Handbook, Seventh Edition. Champaign, IL, 1994.9-5

Additional Inhalation Toxicity Data will not impact risk assessments of Linuron

Inhalation exposure does not add a significant amount to the linuron risk assessment as described in the RED for the uses of linuron supported by TKI. The unit dermal exposure versus the unit inhalation exposure was 0.014 versus 0.0004 mg/lb a.i. or 1:0.028. Inhalation exposure contributed only 3% to the potential linuron exposures and therefore to the risk assessment. In addition, the results of the two repeated dose inhalation studies described above can be used by EPA for modifying the risk assessments described in the RED, if EPA chooses to do so.

Conclusions

TKI believes that a waiver for the 28-day inhalation study is justified based on:

1. Linuron has favorable acute inhalation toxicity characteristics. In the Scoping Document, the Agency indicates linuron is Toxicity Category IV for acute inhalation toxicity.
2. Linuron has a low vapor pressure and is not anticipated to be available for inhalation exposure;
3. The applications methods minimize inhalation exposure. Linuron is a pre and early post emergence herbicide that is applied by ground equipment at low pressure, high water volume, and large droplet sizes. There are no aerial or airblast application uses labeled for Linuron containing formulations.
4. Linuron meets the criteria presently listed by EPA for waiving a repeated dose inhalation toxicity study. It also meets a criterion not listed but indicated by EPA to be a reason for granting a waiver.
5. The toxicity of linuron has been well characterized in various test species. The systems affected to the greatest degree are the hematopoetic and endocrine.
6. An additional repeated dose inhalation toxicity study will not provide any new or more relevant information toward refining occupational risk assessments for inhalation exposure.
7. According to the reregistration evaluation document (RED) for Linuron, the MOEs for occupational exposure are driven by the dermal exposure to Linuron and not to inhalation exposure.
8. Repeat dose inhalation studies already have been submitted to the EPA, including a 14-day and 29-day repeated dose inhalation studies with consistent NOELs and LOELs.
9. From an animal welfare standpoint, the conduct of an additional inhalation toxicity study would be an inappropriate use of additional animals.

Based on the above reasons, TKI respectively request a waiver for a 28-day rat inhalation study on linuron.